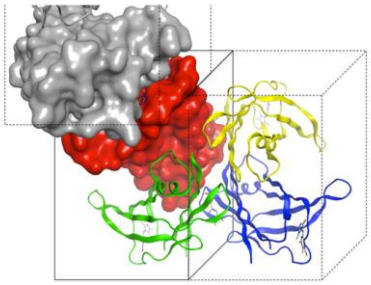
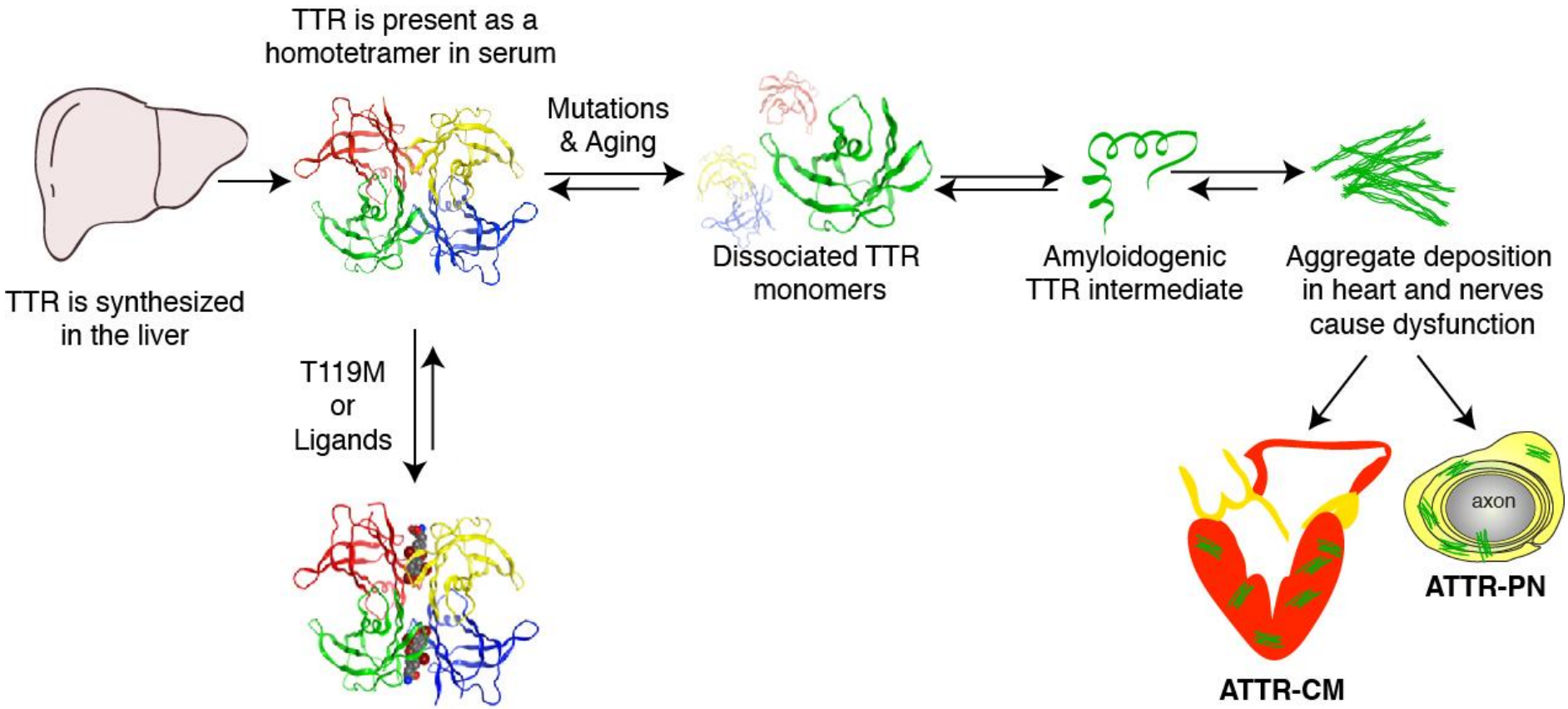
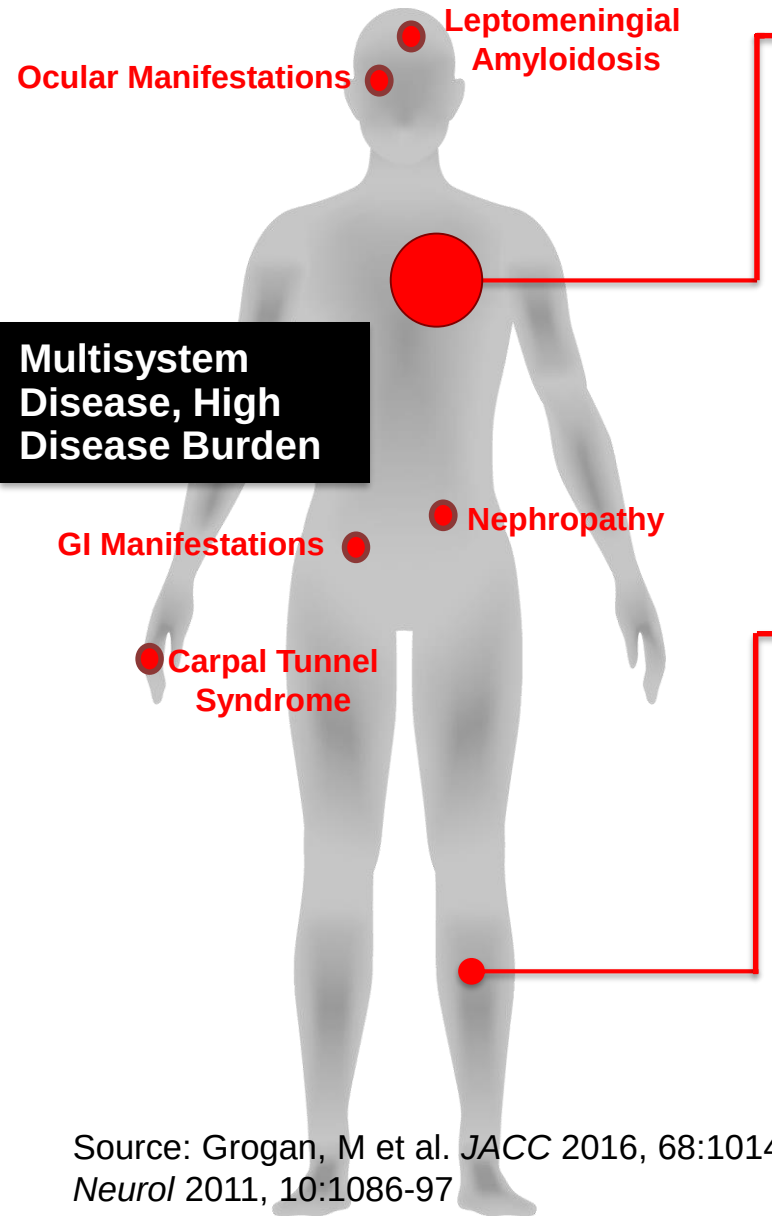


AG10 Stabilizes Pathogenic TTR Variants With High Potency – Potential for an Effective Treatment for ATTR Cardiomyopathy

ATTR-Cardiomyopathy (CM) And ATTR-Polyneuropathy (PN) Are Caused By Aggregation Of Misfolded TTR Monomers



TTR amyloidosis is a systemic disorder



ATTR cardiomyopathy (ATTR-CM)

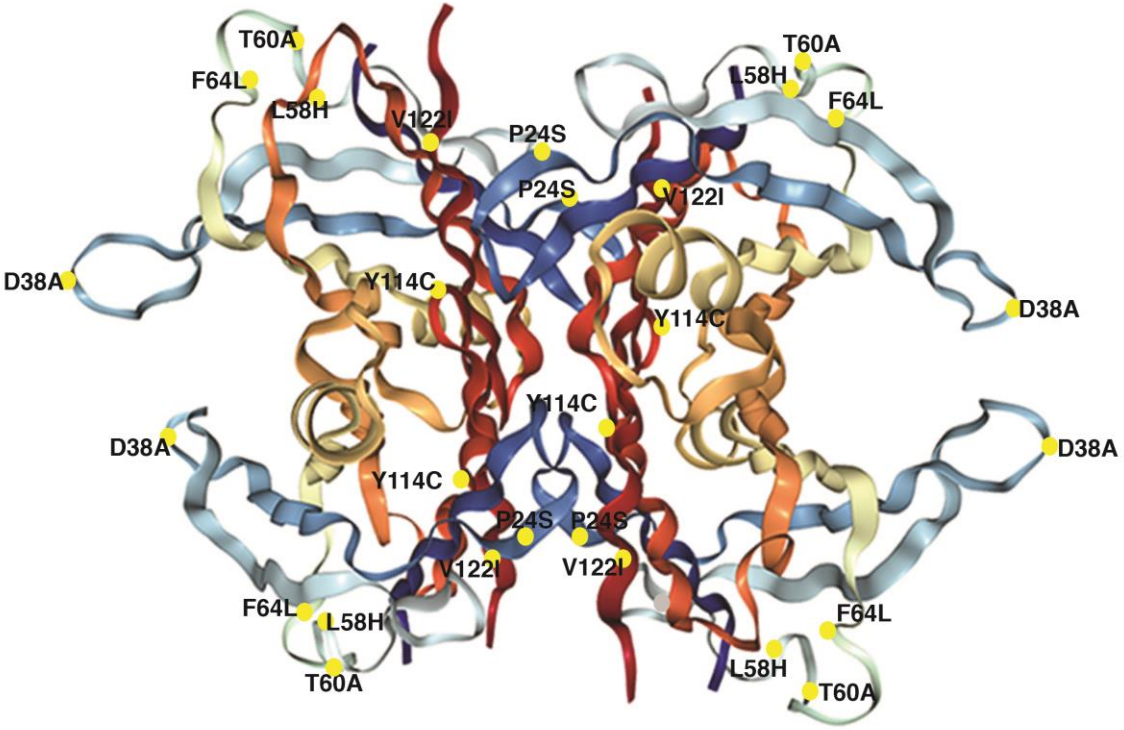
- Deposition of mutant (i.e. V122I) or wild-type TTR amyloid in the heart
  - Leads to predominantly diastolic heart failure
  - Afib/stroke and heart block frequently seen
- Affects > 200,000 patients worldwide
- Late onset (50-60+), death within 4-6 years
- No FDA approved treatment

ATTR polyneuropathy (ATTR-PN)

- Affects ~10,000 patients worldwide, mostly EU &Japan
- Deposition of mutant TTR (i.e.V30M) amyloid in peripheral nerves
  - Autosomal dominant with variable penetrance
  - Leads to sensorimotor & autonomic deficits
- No FDA-approved treatments

Source: Grogan, M et al. *JACC* 2016, 68:1014-20; Planté-Bordeneuve, V. et al, *Lancet Neurol* 2011, 10:1086-97

Does AG10 Stabilize a Broad Range of Pathogenic TTR Variants?



V122I: Cardiomyopathy

T60A: Cardiomyopathy & polyneuropathy

P24S: Cardiomyopathy & polyneuropathy

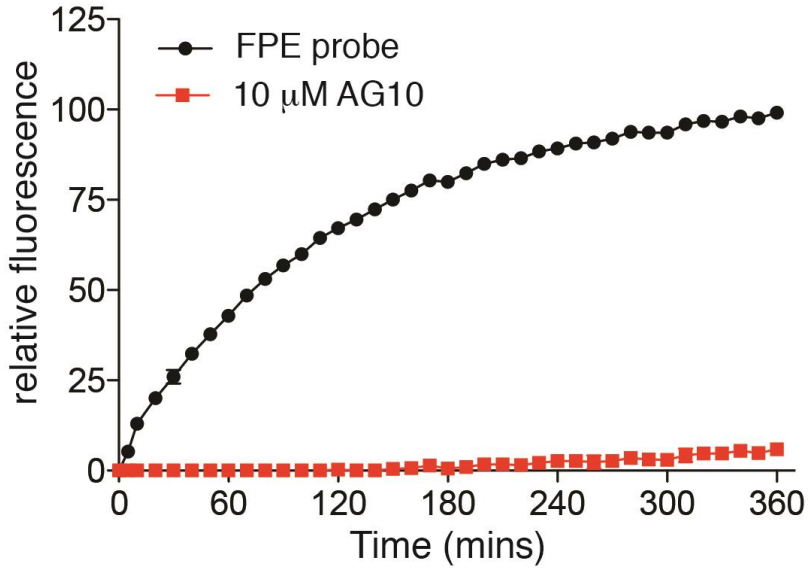
D38A: Cardiomyopathy & polyneuropathy

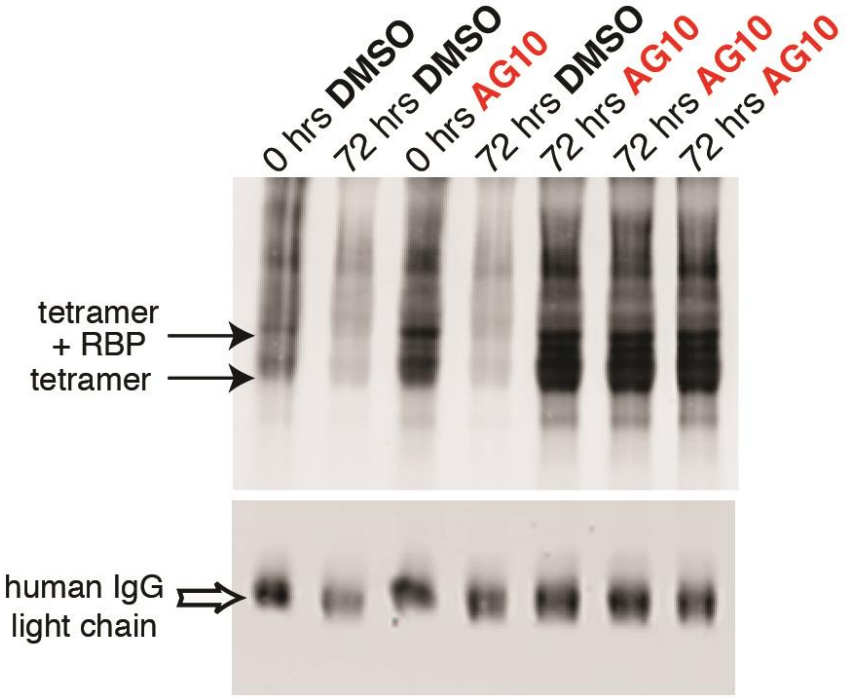
L58H: Cardiomyopathy &polyneuropathy

F64L: Polyneuropathy

Y114C: Polyneuropathy with leptomeningeal complications

AG10 Stabilizes Mutant TTR from V122I ATTR Patients

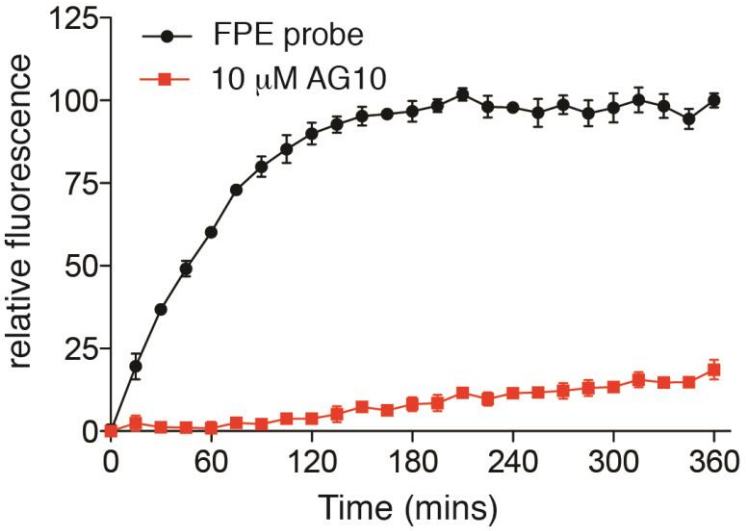


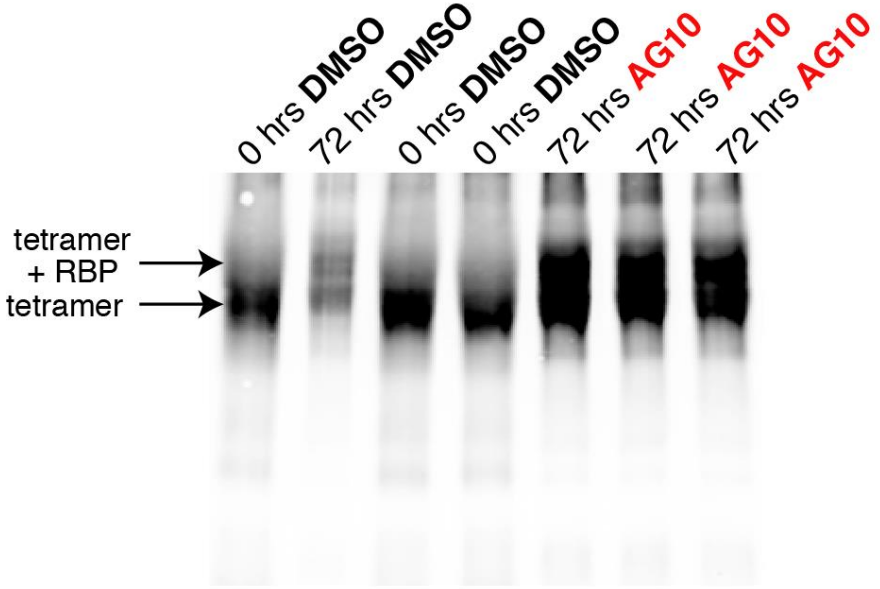


FPE Assay: Change in fluorescence due to modification of TTR in human serum by a covalent probe, which becomes fluorescent following binding to TTR. The lower the binding of the probe/fluorescence the higher the binding selectivity and affinity of the ligand to TTR.

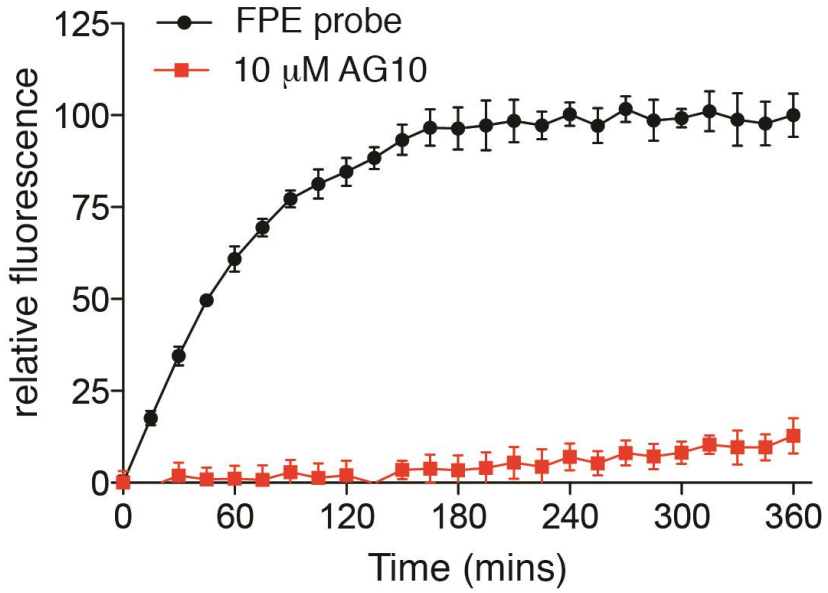
AG10 was used at 10 μM

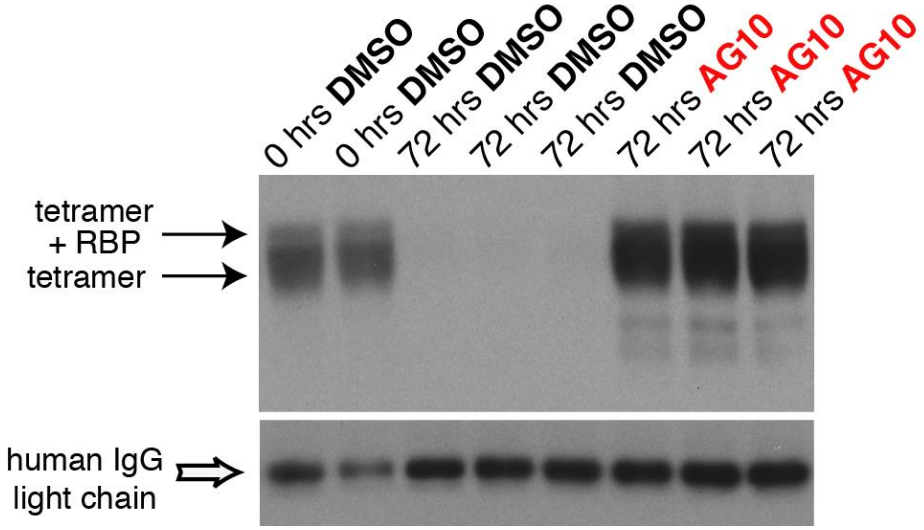
AG10 Stabilizes Mutant TTR from T60A ATTR Patients



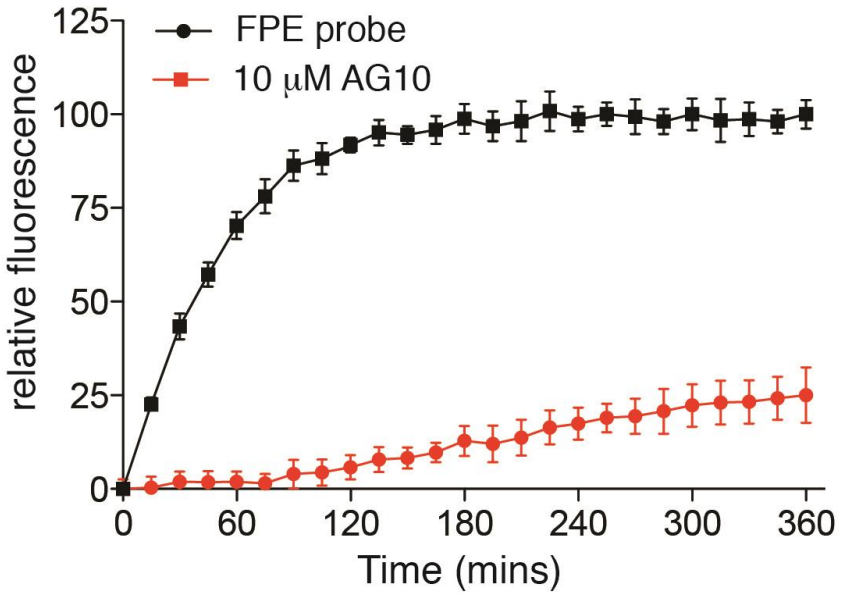


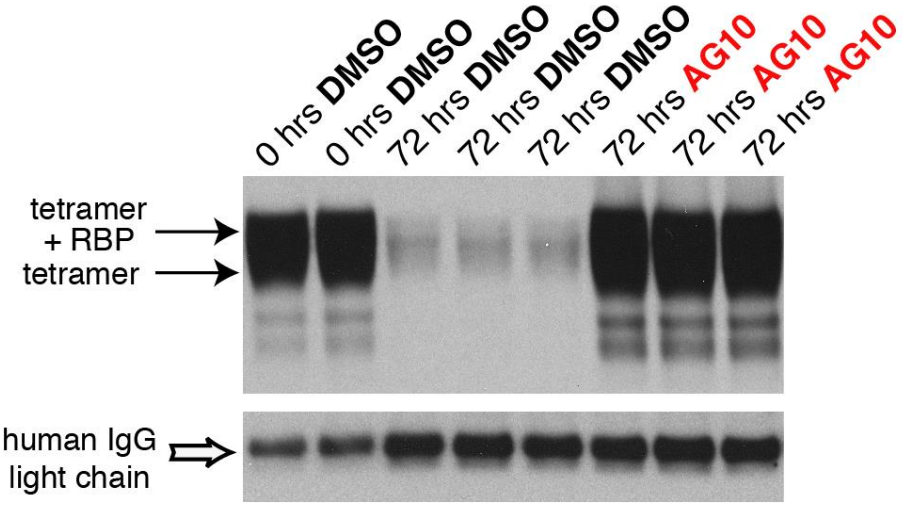
AG10 Stabilizes Mutant TTR from P24S ATTR Patients



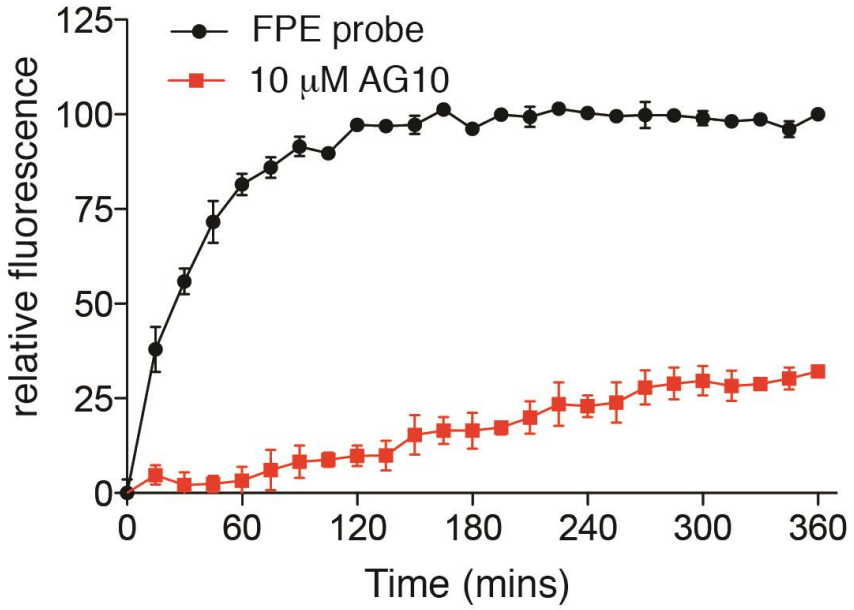


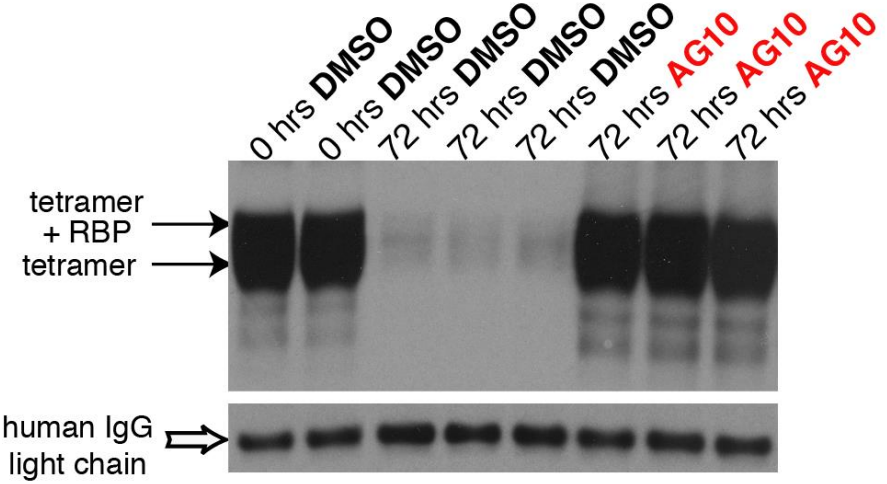
AG10 Stabilizes Mutant TTR from D38A ATTR Patients



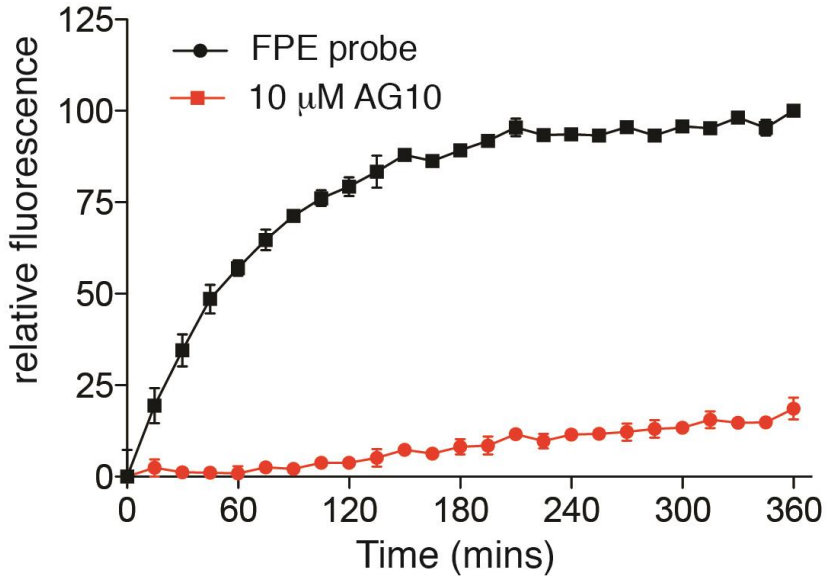


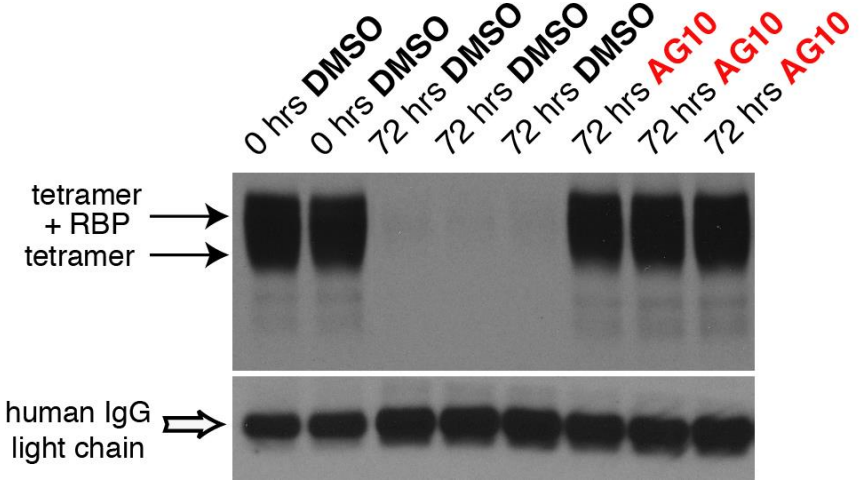
AG10 Stabilizes Mutant TTR from L58H ATTR Patients



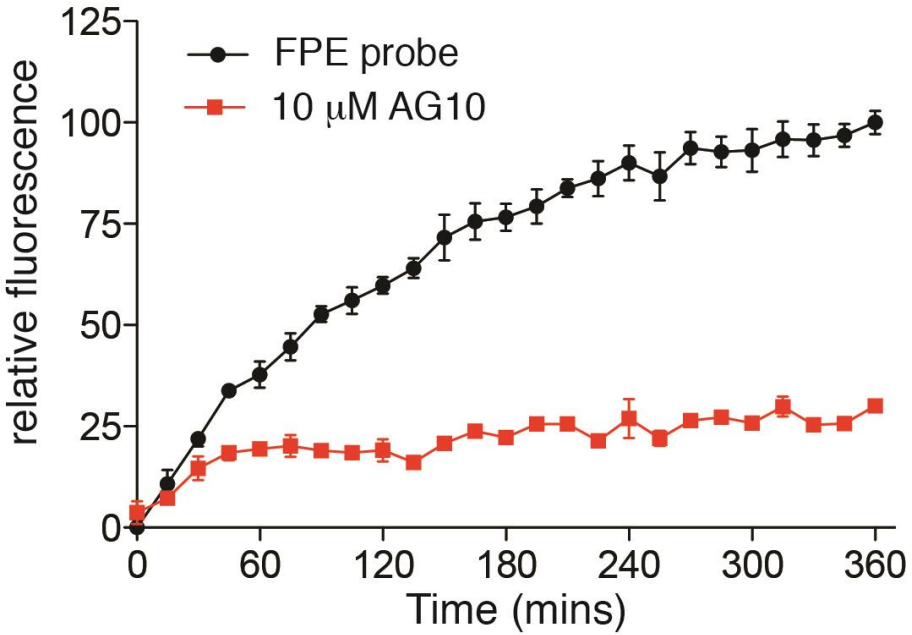


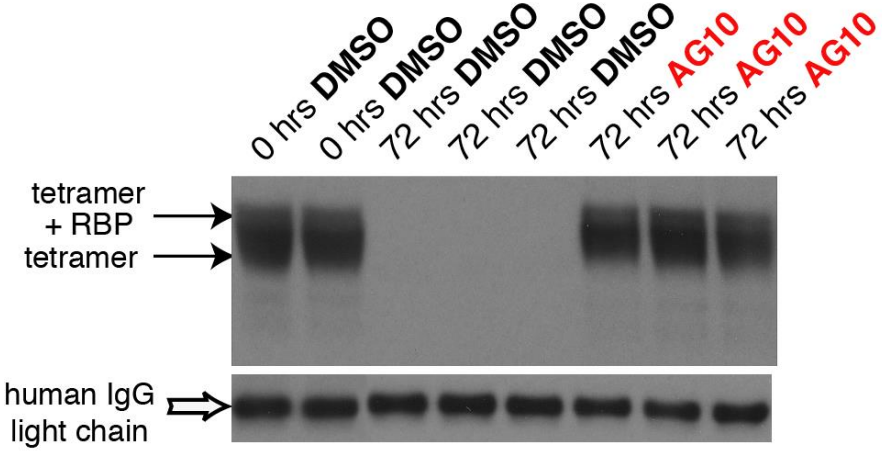
AG10 Stabilizes Mutant TTR from F64L ATTR Patients



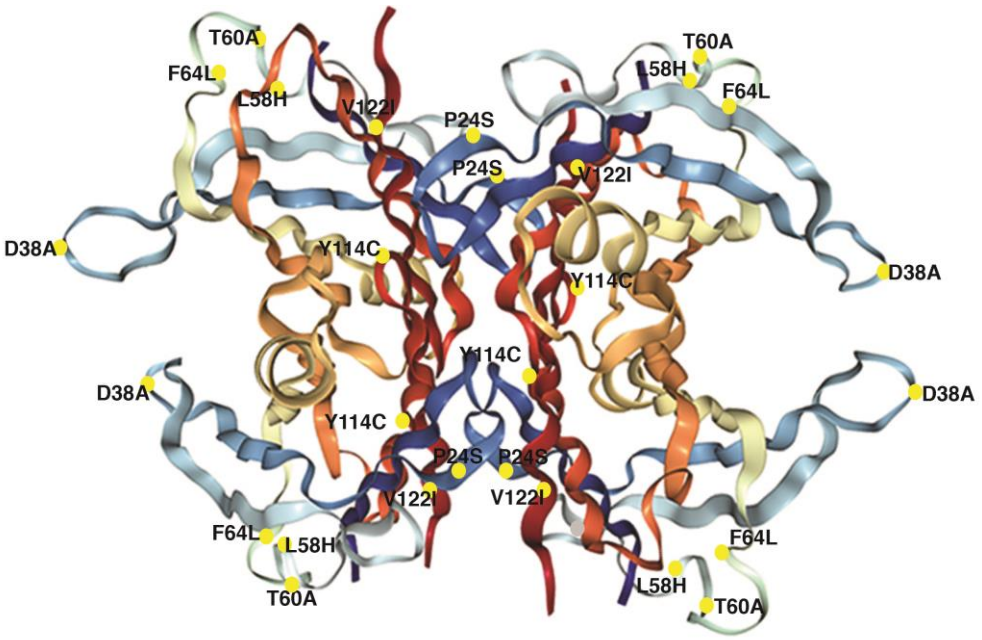


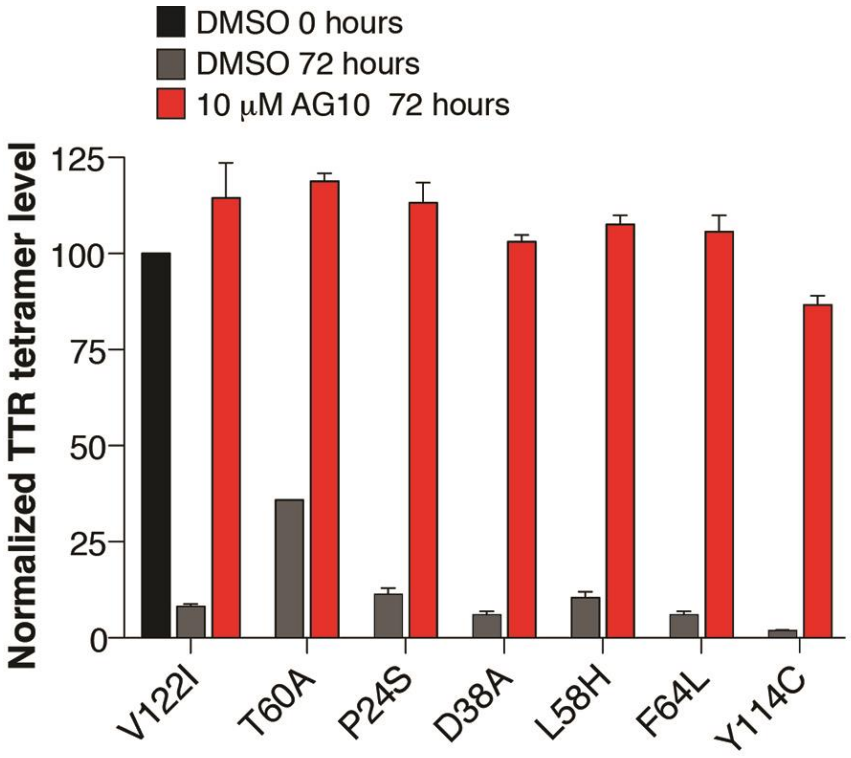
AG10 Stabilizes Mutant TTR from Y114C ATTR Patients





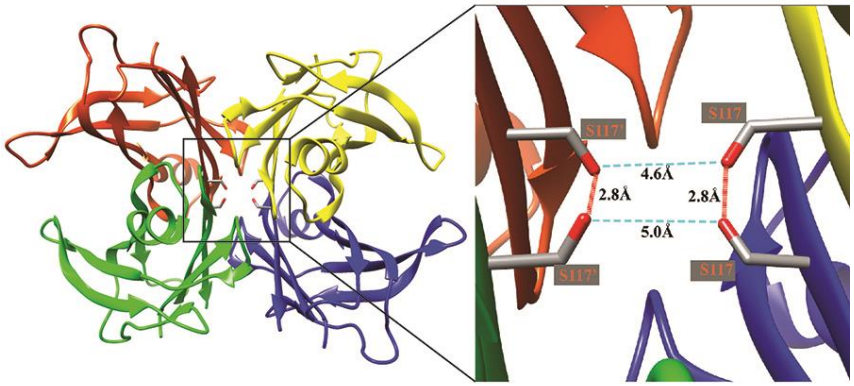
Does AG10 Stabilize a Broad Range of Pathogenic TTR Variants? - YES





AG10 has a unique binding mode, which mimics the effect of the TTR trans-suppressor mutation - T119M

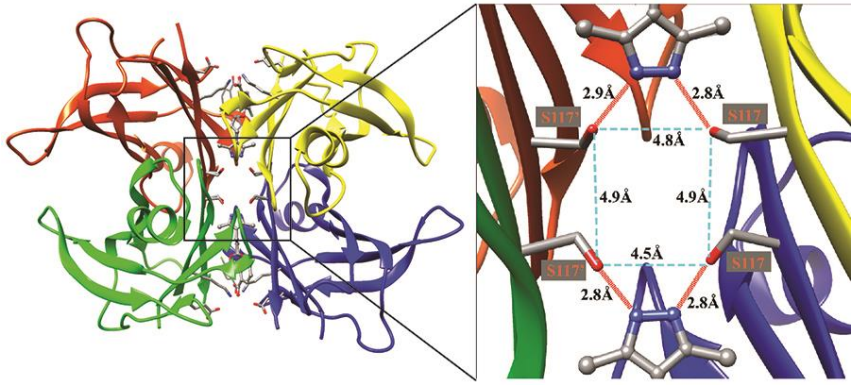
The naturally occurring trans-suppressor mutation T119M super-stabilizes TTR



- The T119M polymorphism creates H-bonds within the complex that super-stabilize the TTR tetramer and functions as a trans-suppressor mutation in V30M carriers.
- T119M heterozygotes have a 5-10 year longer life-span and significantly lower risk of cerebrovascular disease

Hammarström et al, *Science*, 2001, 293:2459-62
Hornstrup et al, *Arterioscler Thromb Vasc Biol*, 2013, 33(6), 1441-7
Penchala et al. *Proc Natl Acad Sci USA,* 2013, 110:9992-7

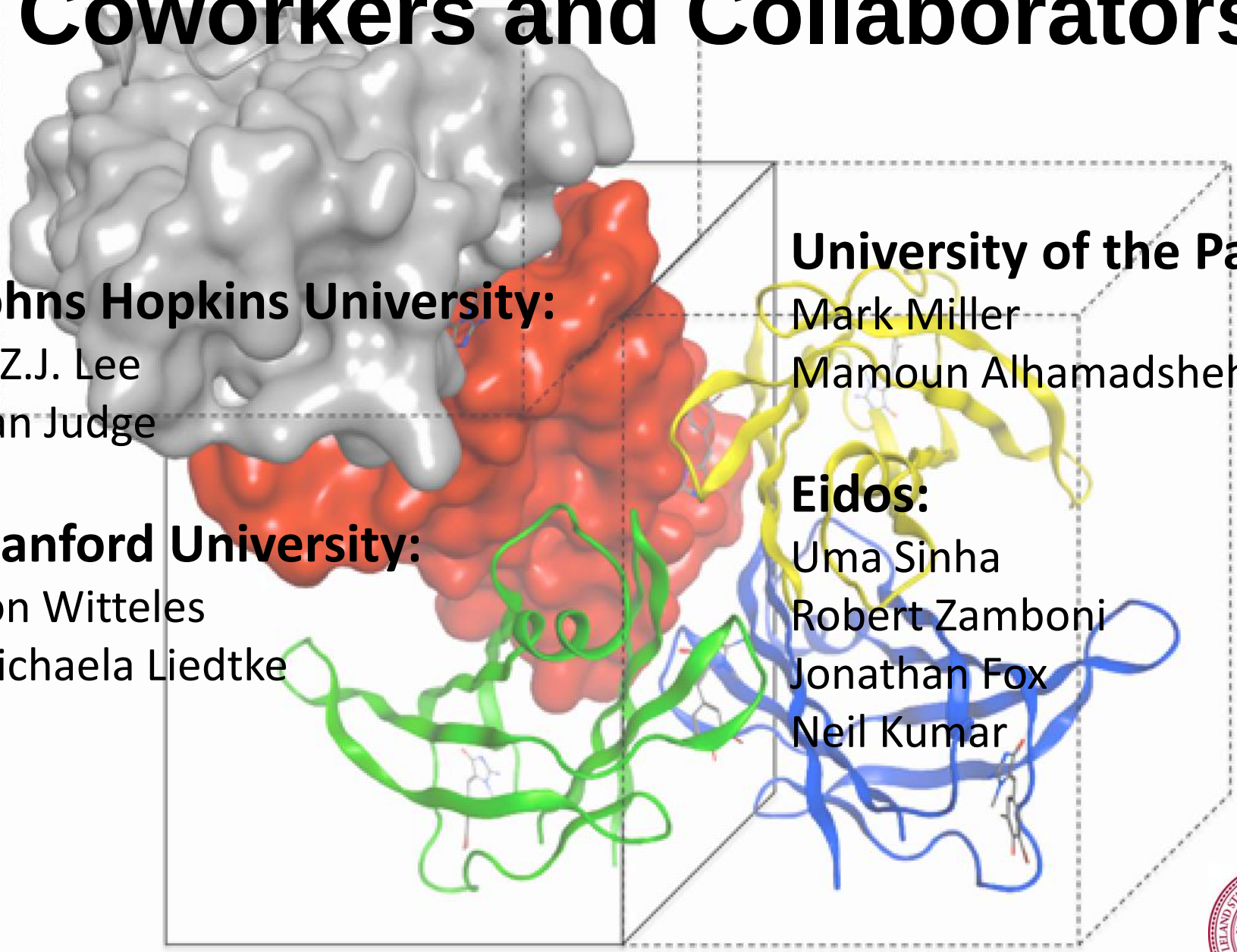
AG10 binding to TTR mimics the stabilizing interactions of T119M variant to S117



- AG10 mimics the structural effects of T119M.
- Stabilization of TTR by AG10 may mimic the clinical effect and lead to improved outcomes

Sebastiao et al, *J. Mol.Biol*. 2001, 306, 733-44
Miller et al, unpublished data

Coworkers and Collaborators



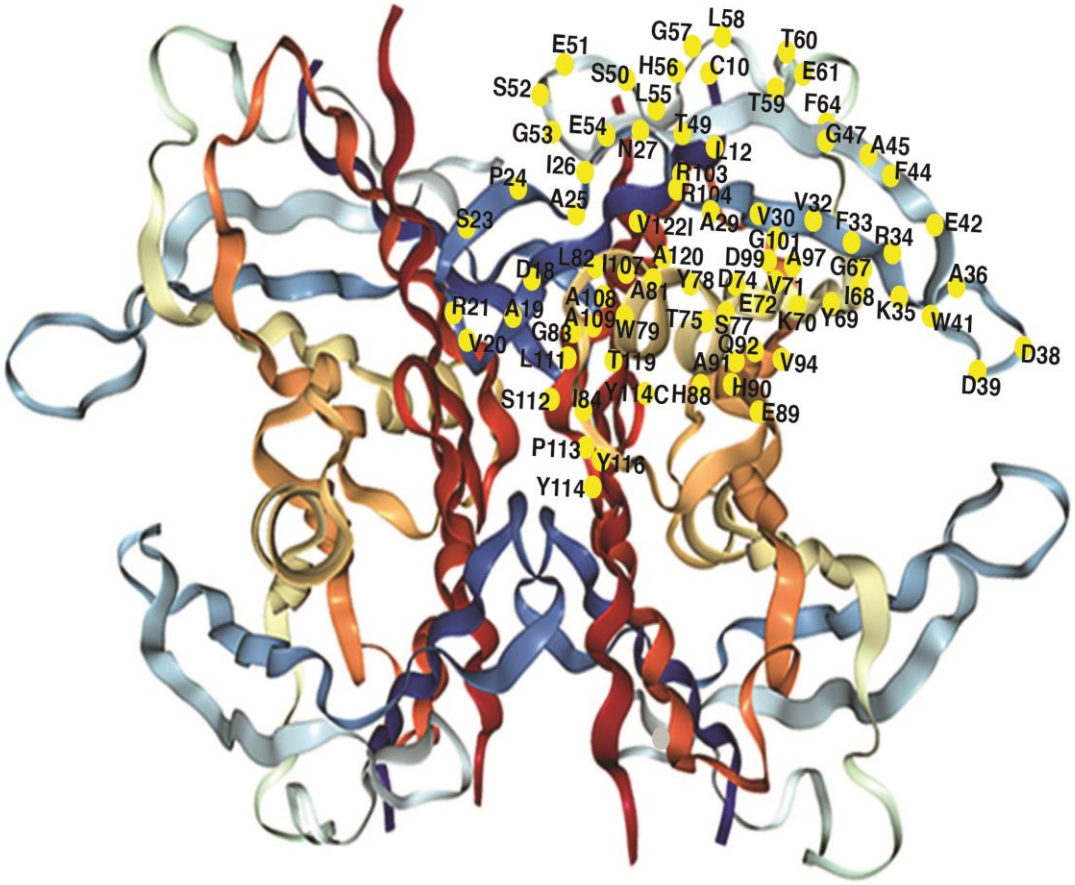
Johns Hopkins University:
Yi Z.J. Lee
Dan Judge

Stanford University:
Ron Witteles
Michaela Liedtke

University of the Pacific:
Mark Miller
Mamoun Alhamadsheh

Eidos:
Uma Sinha
Robert Zamboni
Jonathan Fox
Neil Kumar

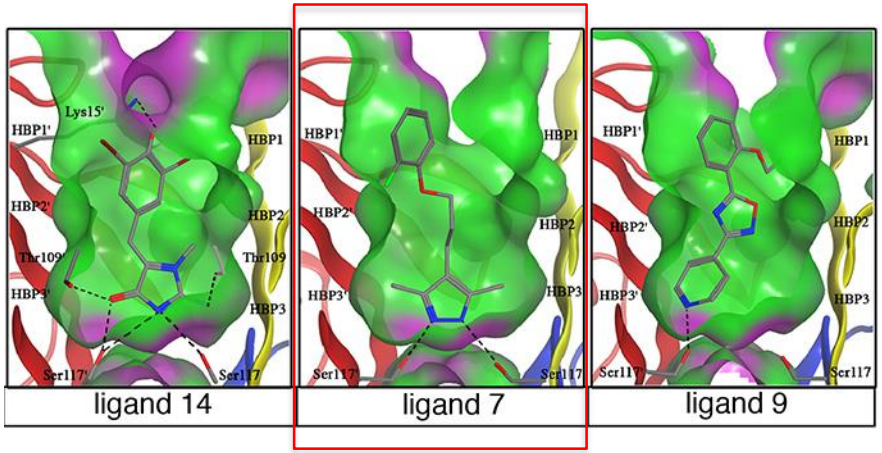
TTR Mutations



- > 100 mutations in the TTR gene have been found to cause TTR amyloidosis (ATTR).
- Most of these alter the TTR structure, resulting in either kinetic or thermodynamic destabilization
- The most common ATTR mutations are V122I (3.4% of African Americans) and V30M.

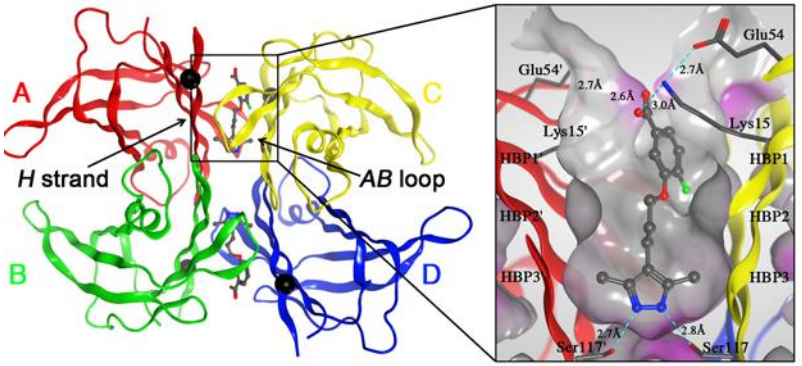
Discovery and Development of AG10

- HTS of 130,000 identified 32 compounds with IC50 <1 μM
- Crystal structure of top novel ligands



- The crystal structure of Ligand 7 was used as a starting point for SAR studies.

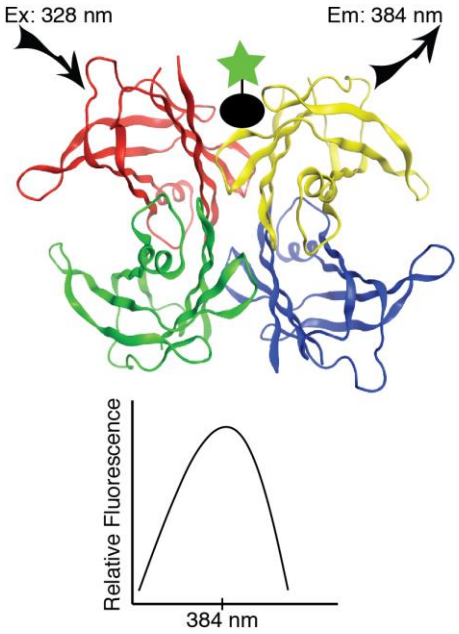
- AG10 was the most potent analogue with the best physicochemical properties



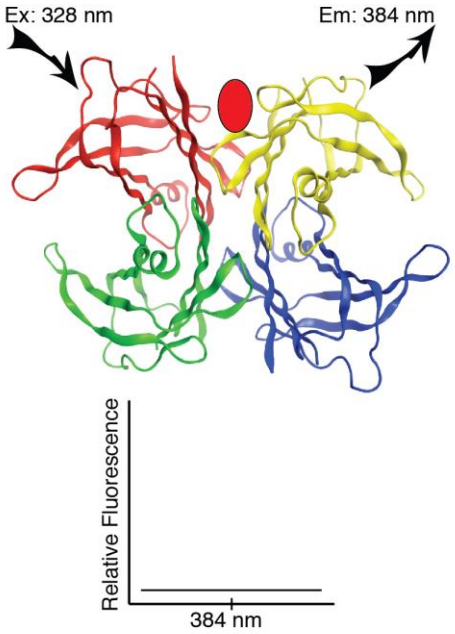
- AG10 was selected for ADME and Toxicity studies
- IND was filed in August 2017 and Phase 1 clinical studies started in September 2017

Alhamadsheh et al, *Science Transl Med,* 2011, August 24, Vol.97
Penchala S. et al. *Proc Natl Acad Sci USA*, 2013, 110:9992-7

AG10 binds with high affinity and high selectivity to human serum TTR



No or low affinity TTR ligand:
covalent probe forms an amide bond with Lys-15 of TTR, creating a fluorescent conjugate.



High affinity/selectivity TTR ligand
competes effectively with the FPE probe and prevents the formation of a fluorescent conjugate.